www.medscape.com

Intranasal Ketamine Succeeds for Resistant Depression in Phase 3 Trial

Deborah Brauser

May 11, 2018

NEW YORK — Administering intranasal esketamine (Janssen) plus an antidepressant is safe, effective, and well tolerated in adult patients with treatment-resistant depression (TRD), a new phase 3 trial suggests.

Dr Vanina Popova

In the global study, those who received a newly initiated oral antidepressant combined with esketamine nasal spray (56 or 84 mg) showed a 4-point greater improvement from baseline to 4 weeks on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score than those who received an antidepressant plus placebo, meeting the study's primary endpoint.

In addition, the response rate was nearly 70% for the study-drug group, while the remission rate was almost 53%.

Adverse events (AEs) commonly reported by this group included nausea, dizziness, vertigo, and a metallic taste.

"Patients treated with esketamine experienced a reduction in depressive symptoms that was rapid, statistically significant, and clinically meaningful compared with those who received the standard of care," presenting author Vanina Popova, MD, study-responsible physician at Janssen Research and Development, Belgium, told *Medscape Medical News* here at the American Psychiatric Association (APA) 2018 annual meeting.

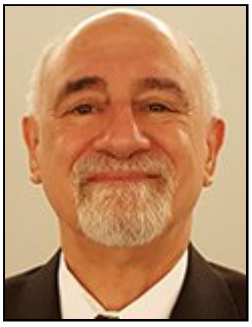
Compared with the 4-point difference they found on the MADRS, Popova noted that "currently available antidepressants typically have a difference vs placebo of 2 to 3 points."

Game Changer?

Asked to comment, APA Secretary Philip Muskin, MD, New York–Presbyterian Hospital and professor of psychiatry at Columbia University Medical Center in New York City, noted that "this was an interesting and novel approach" to treating a difficult patient population.

"And the results were impressive. Not only did they see a response quickly, which is great, they saw it persist, which is even greater," Muskin told *Medscape Medical News*.

"They also saw very impressive remission rates, at around 52%. Remission means 'you're well,' and is what we shoot for in everything every physician treats," Muskin said.



Dr Philip Muskin

He noted that although ketamine has been shown to be effective in some patients with depression, "it comes with side effects. It's a psychoactive drug that some people are uncomfortable with; the only way we can give it is intravenously; and for the majority of people, the effect doesn't persist.

"So here's a nasal spray that is a left-handed isomer of ketamine. And it turns out that this left-handed molecule does not have the psychoactive effects, the psychosis, disassociation, etc, as far as we know," said Muskin. He added that the delivery system is also a lot more convenient.

Although subanesthetic doses of intravenous ketamine have been shown to "exhibit robust and rapid onset of efficacy in patients with TRD," it hasn't been especially convenient, note the investigators.

Esketamine, a glutamatergic *N*-methyl-D-aspartate receptor antagonist, is an S-enantiomer of ketamine racemate. The US Food and Drug Administration (FDA) issued a breakthrough therapy designation for the intranasal drug in November 2013 for TRD. The agent also received this designation in 2016 for treating major depressive disorder associated with imminent risk for suicide.

As reported by *Medscape Medical News*, earlier this year, a phase 2 trial with almost 70 patients with TRD showed that those who received 56 mg of intranasal esketamine plus an oral antidepressant demonstrated a 7-point change between baseline and day 8 on the MADRS total score compared with those who received placebo; patients who received a dose of 84 mg demonstrated a 10-point change.

Sustained improvement in depressive symptoms was shown for up to 2 months after treatment ended.

Primary Outcome Met

In the current trial, the investigators enrolled more than 200 patients aged 18 to 64 years at 39 sites in the United States, Germany, Poland, Spain, and the Czech Republic. All of the participants had not responded to at least two previous antidepressants

Between August 2015 and June 2017, patients were randomly assigned to receive daily for 4 weeks a newly initiated open-label antidepressant plus either intranasal esketamine twice weekly (starting at 56 mg, with the possibility of an increase to 84 mg; n = 114) or matching intranasal placebo (n = 109).

The mean age for each treatment group was 44.9 and 46.4 years, respectively; women constituted 65.8% and 57.8% of the groups, respectively. All of the participants had moderate to severe TRD, with mean baseline MADRS scores of 37.0 and 37.3, respectively.

At the end of treatment, 66.7% of the esketamine group were receiving the drug at 84 mg. Follow-up for all patients continued to week 24.

The treatments were provided in disposable nasal spray devices under a healthcare professional's supervision. To simulate the taste of esketamine, a bittering agent was added to placebo.

The open-label oral antidepressant was chosen by an investigator from among four possibilities: duloxetine (*Cymbalta*, Lilly), escitalopram (*Lexapro*, Allergan), sertraline (*Zoloft*, Pfizer), or venlafaxine extended release (*Effexor XR*, Wyeth). Its dosing followed a fixed titration schedule.

The primary efficacy endpoint (change from baseline to day 28 on the MADRS total score) was significantly greater for the active nasal-treatment group compared with the placebo group (adjusted mean difference, -4.0; 95% confidence interval [CI], -7.31 to -0.64; 1-sided *P* = .01).

"Response was rapid in onset and increased over time during repeated dosing," write the investigators.

Although not statistically significant, more members of the study-drug group achieved at least 50% improvement over baseline MADRS total score at 24 hours post administration, which was maintained to day 28 (7.9% vs 4.6%, respectively).

Because a mixed-effects model with repeated measures (MMRM) was employed, this first key secondary endpoint needed to be significant in order for the other two key secondary efficacy endpoints to be "formally evaluated."

Thus, although change from baseline to week 4 on total score of the Patient Health Questionnaire was greater for those who received esketamine (difference of least square [LS] means, -2.4; 95% CI, -4.18 to -0.69; *P* = .003), it was not considered statistically significant.

The same was true for change from baseline to week 4 on the total score of the Sheehan Disability Scale (difference of LS means, -4.0; 95% CI, -6.28 to -1.64; *P* < .001).

More of the patients who received esketamine achieved remission, defined as a MADRS total score of 12 or less at day 28, than those who received placebo (52.5% vs 31.0%, respectively;*P* = .001). Response rate, defined as achieving at least a 50% improvement over baseline on the MADRS, was achieved by 69.3% vs 52.0% of the groups, respectively.

A New Approach for Depression?

The most frequently reported AEs during the treatment phase were nausea and vertigo (each reported by 26.1% of the esketamine group vs 6.4% and 2.8% of the placebo group).

Other commonly reported AEs included dysgeusia (24.3% vs 11.9% of the groups, respectively), dizziness (20.9% vs 4.6%), and headache (20.0% vs 17.4%).

In addition, there was a transient increase in blood pressure (BP) up to 40 minutes after administration of each dose of esketamine. BP usually returned to preadministration ranges 1.5 hours after dosing.

"Most adverse events...subsided spontaneously by 60 to 90 minutes post dose," said Popova. In addition, "there was no pushback" in regards to the nasal delivery system. "The route of administration was well received, and it was certainly more convenient than intravenous administration," she said.

Overall, the "favorable safety and tolerability...reported in this study suggest a positive risk-benefit profile," write the investigators.

In addition, the study "marks the first time an antidepressant has achieved superiority in a clinical trial for major depressive disorder that included a newly initiated oral antidepressant in both the control and placebo groups," the manufacturer noted in a press release.

If approved by the FDA, the drug "would be one of the first new approaches to treat refractory major depressive disorder available to patients in the last 50 years," they added.

A representative for Janssen told *Medscape Medical News* that the company will be presenting additional long-term safety and relapse-prevention findings for the drug at the American Society of Clinical Psychopharmacology 2018 annual meeting in Miami, Florida. It also plans to file new drug applications in the United States and Europe by the end of this year.

"Especially Impressive" Results

Muskin noted that the 4-point difference found on the MADRS would be good in any patient group but was especially impressive in those with TRD.

"We don't know yet whether using ketamine should be used as a first-line treatment. I think that particular research is yet to establish itself," said Muskin. "But if someone gets depressed and the first thing you should do is to have intranasal esketamine or one of the other analogues that drug companies are working on, that may change the way we treat patients."

He also noted that the treatment-related AEs in this study "weren't particularly obnoxious" and were temporary, in

contrast to the persistent AEs associated with other antidepressants. "So I think this is very exciting," he said.

That said, Muskin noted that, with a study population of only around 200, "you can't say: this is it. More research is needed," including assessment of further dosing strategies and possible long-term psychiatric AEs.

In addition, he said that, if approved, insurance reimbursement will be important — especially in the age of so-called "three and fail" rules. This means a patient has to fail to respond to three different drugs "before they're given the definitive treatment," he said. Muskin also questioned how many drugs would need to fail a patient with TRD before insurers would pay for this drug.

"My concern is, what will the cost be? And what will the pickup be by the insurance companies?" he asked.

"But if this becomes an FDA-approved treatment for depression, even if insurers don't pay the entire cost of treatment, it will defray the cost for people. Giving struggling patients hope that there are things in the pipeline is important," said Muskin.

Phase 3 in Older Patients

A separate phase 3 study that was presented at the meeting assessed the use of intranasal esketamine in older patients with TRD. That study just missed its primary endpoint of change on the MADRS total score from day 1 to the end of 4 weeks.

All participants were at least 65 years of age (mean age, 70.0 years; mean baseline MADRS total score, 35.2). They were randomly assigned to receive a new oral antidepressant plus either flexibly dosed esketamine at 28, 56, or 84 mg (n = 72) or matching placebo (n = 66).

MMRM analysis needed a one-sided .025 level to signify statistical significance. Although the change in MADRS total score from baseline to day 28 was greater in the study-drug group than in the placebo group (-10 vs -6.3, respectively), the "median unbiased estimate of difference" was -3.6 (95% CI, -7.2 to 0.07; one-sided *P* = .029).

"Although it didn't make the primary, it was very close," presenting author Rachel Ochs-Ross, MD, medical director of neurosciences for Janssen Research and Development, Pennington, New Jersey, told *Medscape Medical News*.

Dr Rachel Ochs-Ross

"We started with a low dose in this elderly study at 28 mg, which isn't actually an efficacious dose. And we also allowed investigator discretion for titration up or down, based on tolerability and efficacy," she said.

Ochs-Ross added that this study population is known for having comorbidities, which may have had an impact.

"Still, we did see a 3.6-point difference, and that is clinically meaningful," she said.

Additional Analyses

In prespecified subgroup analyses, the participants aged 65 to 74 years who received esketamine experienced a significantly greater change in MADRS total score at day 28 than those who received placebo (difference in LS means change, -4.9; one-sided *P* = .009). However, there were no significant treatment-related differences in the subgroup that was aged 75 or older (difference, -0.4).

The response rate for the full group that received esketamine was 27.0%, vs 13.3% for the placebo group. Remission rates were 17.5% and 6.7%, respectively.

The most commonly reported treatment-emergent AEs were dizziness (20.8 vs 7.7 of the groups, respectively), nausea (18.1% vs 4.6%), blood pressure increase (12.5% vs 4.6%), and fatigue (12.5% vs 7.7%).

Three patients in the esketamine group reported a serious AE (anxiety, increased blood pressure, and hip fracture), compared with two patients in the placebo group (feelings of despair and gait disturbance/dizziness). "All were resolved by the end of the study," report the investigators.

There were no deaths and no significant changes in electrocardiogram results, laboratory evaluations, nasal tolerability, or sense of smell, nor were there decreases in respiratory rates.

"This is a tough group, and elderly people have different brains," commented Muskin.

Regarding missing the primary outcome, "it could be a neurotransmitter issue, but you don't really know," he said.

"It could be that this just doesn't work in the elderly, or it could be the dosing or timing strategy," he added. "Some people might need it once a day, some might need it once a week. We just don't know — but that's what further research is for."

Ochs-Ross reported that further analyses will be conducted on this population's data. "This is a neglected, hard-to-treat population, and yet we saw a clinically meaningful response from them. To me, that's a hopeful message," she said.

The studies were funded by Janssen. Dr Popova is an employee of Janssen Research and Development and holds company equity. Dr Ochs-Ross is also an employee of the company and holds company stock and/or stock options. Dr Muskin has disclosed no relevant financial relationships.

American Psychiatric Association (APA) 2018. Abstracts P7-065 and P8-054, presented May 8, 2018.

Follow Deborah Brauser on Twitter: @MedscapeDeb. *For more Medscape Psychiatry news, join us on* Facebook *and* Twitter.

Cite this article: Intranasal Ketamine Succeeds for Resistant Depression in Phase 3 Trial - *Medscape* - May 11, 2018.